(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 345 593 A1**

(12) EUROPEAN PATENT APPLICATION

(21) Application number: 89109679.4

(22) Date of filing: 30.05.89

(51) Int. Cl.4: C07D 307/79 , C07D 307/92 , //A61K31/34

(30) Priority: 10.06.88 JP 143859/88

(43) Date of publication of application: 13.12.89 Bulletin 89/50

(84) Designated Contracting States: AT BE CH DE ES FR GB GR IT LI LU NL SE

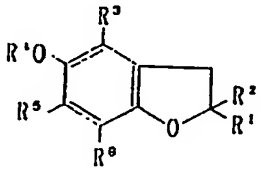
(71) Applicant: TAKEDA CHEMICAL INDUSTRIES, LTD.
3-6, Doshomachi 2-chome Chuo-ku
Osaka 541(JP)

(72) Inventor: Goto, Gichi
6-11, Kofudai 5-chome Toyono-cho
Toyono-gun Osaka 563-01(JP)
Inventor: Ohkawa, Shigenori
45-20, Makamicho 6-chome
Takatsuki Osaka 569(JP)
Inventor: Fukuda, Naohisa
1-56, Suimeidai 4-chome
Kawanishi Hyogo 666-01(JP)

(74) Representative: Lederer, Franz, Dr. et al
Van der Werth, Lederer & Riederer
Patentanwälte Lucile-Grahn-Strasse 22
D-8000 München 80(DE)

(54) 2-substituted coumaran derivatives.

(57) The present invention relates to a compound of the formula:



(I)

wherein R^1 is hydrogen or a lower alkyl; R^2 is methyl which is substituted by a carboxy, alkoxycarbonyl, cyano, halogen, aryl or heterocyclic group or C_{2-15} chain-like hydrocarbon residue having no lower alkyl at the a-position which may be substituted by a carboxy, alkoxycarbonyl, cyano, halogen, aryl or heterocyclic group; R^3 is a lower alkyl; R^4 is hydrogen or acyl; and R^5 and R^6 each is a lower alkyl or lower alkoxy, or R^5 and R^6 combinedly are butadienylene or a salt thereof.

The compound (I) of the present invention has a strong 5- and 12-lipoxygenase inhibiting action, is of high safety and is useful as, among others, an agent for ameliorating circulatory system, an anti-allergic agent and a pharmaceutical agent for central nervous system

EP 0 345 593 A1

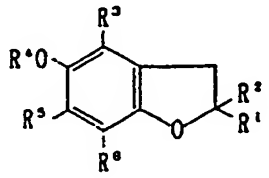
2-Substituted Coumaran Derivatives

This invention relates to 2-substituted coumaran derivatives.

While several types of compounds of coumaran derivatives have been synthesized [Journal of American Chemical Society (J. Am. Chem. Soc.) 105, 5950(1983); ibid, 107, 7053(1985)], substantially no reports have been made on their pharmacological actions.

The present inventors synthesized various types of coumaran derivatives and found that they had inhibitory actions on 5-lipoxygenase and 12-lipoxygenase participating in the biosynthesis of leucotrienes and lipoxins, and they have continued the research work diligently to accomplish the present invention.

The present invention is to provide a compound of the formula:



(I)

wherein R^1 is hydrogen or a lower alkyl; R^2 is methyl which is substituted by a carboxy, alkoxycarbonyl, cyano, halogen, aryl or heterocyclic group or C_{2-15} chain-like hydrocarbon residue having no lower alkyl at the a-position which may be substituted by a carboxy, alkoxycarbonyl, cyano, halogen, aryl or heterocyclic group; R^3 is a lower alkyl; R^4 is hydrogen or acyl; R^5 and R^6 each is a lower alkyl or lower alkoxy, or R^5 and R^6 combined are butadienylene, and a salt thereof.

Referring to compounds represented by the above-mentioned (I), the lower alkyl represented by R^1 is exemplified by C_{1-6} alkyl such as methyl, ethyl, propyl, i-propyl, butyl, i-butyl, sec-butyl, t-butyl, amyl, hexyl, etc., especially C_{1-3} alkyl (methyl, ethyl, propyl, i-propyl, etc.) being preferable.

As substituents of the substituted methyl represented by R^2, mention is made of aryl (phenyl, 1-naphthyl, 2-naphthyl, indanyl, tetralyl, etc.), heterocyclic group (2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 1-imidazolyl, 5-thiazolyl morpholino, thiomorpholino, etc.), halogen (fluorine, chlorine, bromine, iodine), carboxyl, alkoxycarbonyl (preferably C_{2-5} ones such as methoxycarbonyl, ethoxycarbonyl, etc.), cyano, etc. Further, the aryl and the heterocyclic groups may have one to two or more substituents at an optional position of the ring. As the said substituents, mention is made of, for example, unsubstituted C_{1-20} alkyl (e.g. methyl, ethyl, propyl, isopropyl, butyl, t-butyl, pentyl, hexyl, octyl, nonyl, decyl, undecyl, dodecyl, tridecyl, tetradecyl, pentadecyl, hexadecyl, heptadecyl, octadecyl, nonadecyl, eicosyl, etc.), lower (C_{1-6}) alkyl optionally substituted with hydroxyl group, carboxyl, C_{2-5} alkoxycarbonyl, piperazyl, phenylthio, etc., C_{2-4}allyl (vinyl, etc.) optionally substituted with carboxyl or alkoxycarbonyl (C_{2-5} alkoxycarbonyl such as methoxycarbonyl, ethoxycarbonyl, etc.), hydroxyl group, halogen (fluorine, chlorine, bromine, etc.), nitro, formyl, C_{1-3} alkoxy (methoxy, etc.), carboxyl, trifluoromethyl, di-C_{1-3} alkylamino, C_{5-7} cycloalkyl, C_{1-3} alkylthio, etc.

As the chain-like hydrocarbon residue having 2 to 15 carbon atoms, which has no lower alkyl on the a-position, represented by R^2, mention is made of straight-chain or branched C_{2-15} chain-like aliphatic hydrocarbon groups, and when it is alkenyl, the number of double bonds is usually 1 to 5, and these double bonds may be conjugated. And, in the case of alkynyl, the number of its triple bonds is 1 to 5.

As the above-mentioned chain-like hydrocarbon residues, those having 2 to 6 carbon atoms are preferable, as exemplified by alkyl such as ethyl, i-propyl, butyl, i-butyl, sec-butyl, t-butyl, pentyl, hexyl, alkenyl such as 1-propenyl, 2-butenyl, 1,3-butadienyl, 2-pentenyl, vinyl, 2-propenyl, isopropenyl, and alkynyl such as ethynyl, 2-propynyl, 2-penten-4-ynyl.

Referring to the substituents of C_{2-15} chain-like hydrocarbon residue represented by R^2, as preferable alkoxycarbonyl, mention is made of C_{2-5} alkoxycarbonyl (methoxycarbonyl, ethyoxycarbonyl, propoxycarbonyl, i-propoxycarboxyl, etc.), and, as halogen, mention is made of fluorine, bromine, chlorine and iodine. As the aryl and heterocyclic groups, mention is made of the respectively those similar to the groups described as above, and, when these groups have further substituents are mentioned those similar to the groups described as above.

Examples of the lower alkyl shown by R^3 include C_{1-6} alkyl such as methyl, ethyl, propyl, i-propyl, butyl, i-butyl, sec-butyl, t-butyl, amyl, hexyl, etc., especially, C_{1-3} alkyls (methyl, ethyl, propyl, i-propyl,

etc.) are preferable.

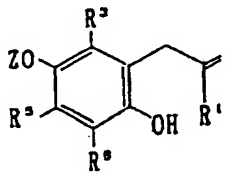
As the acyl shown by R^4, mention is made of acyl carboxylate, acyl sulfonate, acyl phosphate, etc., preferably those having C_{1-10} substituents (methyl, ethyl, propyl, phenyl, etc.). Preferable ones include chain-like (C_{1-10}) or cyclic (C_{3-10}) alkanoyl, such as formyl, acetyl, propionyl, isobutyryl, decanoyl, cyclopentyl or cyclohexylcarbonyl, benzoyl, optionally quaterized nicotinoyl, half ester of succinate, etc.

Examples of the lower alkyl shown by R^5 and R^6 respectively include C_{1-6} alkyl such as methyl, ethyl, propyl, i-propyl, butyl, i-butyl, sec-butyl, t-butyl, amyl, hexyl, etc., especially preferable ones being C_{1-3} alkyl (methyl, ethyl, propyl, i-propyl, etc.). These substituents are exemplified by hydroxyl group, halogen (fluorine, bromine, chlorine, iodine, etc.), nitro, trifluoromethyl, carboxyl, C_{2-5} alkoxycarboxyl (methoxycarbonyl, ethoxycarbonyl, etc.), 3-pyridyl, 1-imidazolyl, 5-thiazolyl, etc. And, examples of the lower alkoxy shown by R^5 and R^6 include C_{1-3} alkoxy such as methoxy, ethoxy, propoxy, i-propoxy, etc.

When R^5 and R^6 combined represent butadienylene, naphthalene ring is formed, and as the substituents on thus-formed benzene ring, are mentioned one to three lower (C_{1-3}) alkyls, lower (C_{1-3}) alkoxy (methoxy, ethoxy, propoxy, etc.), hydroxyl group, nitro, halogen, etc.

The compound (I) may, in accordance with the kinds of substituents thereon, form corresponding salts, and the salts are exemplified by those with an organic acid (e.g. acetic acid, propionic acid, oxalic acid, maleic acid) or an inorganic acid (e.g. hydrochloric acid, sulfuric acid, phosphoric acid, etc.), or those with a base such as an alkali metal (potassium, sodium, etc.), an alkaline earth metal (calcium, magnesium, etc.), ammonia, etc., and, among them, physiologically acceptable ones are especially preferable.

The compound (I) can be produced by, for example, allowing a compound represented by the formula



(II)

wherein R^1, R^3, R^5 and R^6 are of the same meaning defined as above, Z is hydrogen or a hydroxyl-protecting group, to react with halogen molecule in the presence of a base to cause ring-closure, or by subjecting the compound (II) to the treatment with a peracid in the presence of a base to cause ring closure, followed by allowing thus ring-closed compound to react with an oxidizing agent, then subjecting thus-obtained compound to addition-elimination reaction with a compound represented by the formula

$(C_6H_5)_3P^{\oplus}\text{-}R^{2'}X^{\ominus}$ (III)

wherein X is halogen, R^2 is a chain-like hydrocarbon residue whose carbon number is less by one than that of R^2, followed by, when desired, subjecting the resultant to deprotection, acylation, hydrogenation or(and) substituent-exchange reaction, respectively.

As the hydroxyl-protecting group, C_{2-4} alkanoyl such as acetyl, propionyl, etc. is mentioned.

The ring-closure reaction with the aid of halogen is carried out by allowing, for example, bromine to react in an organic solvent such as halogenated carbon (e.g. chloroform, methylene chloride, etc.) or acetic acid, etc. at temperatures ranging from -5° C to 80° C.

And, the cyanation can be carried out, in general, by allowing, for example, sodium cyanate or potassium cyanate to react in a solvent such as dimethyl sulfoxide, dimethyl formamide, etc. at temperatures ranging from 60° C to 100° C for 1 to 24 hours. In this case, the protecting group is hydrolyzed with a small volume of water present in the reaction system to give a 5-hydroxy compound at one stroke.

The ring-closure reaction by the use of a peracid is conducted by using a peracid such as m-chloroperbenzoic acid in an organic solvent such as methyl chloride in the presence of a base such as triethylamine at temperatures ranging from -10° C to 50° C. And, the oxidation is conducted by using an oxidizing agent obtained from dimethyl sulfoxide and oxalyl chloride, chromium trioxide, etc., in an organic solvent such as methylene chloride, acetone, etc., and, when desired, in the presence of a base such as triethylamine, etc., at temperatures ranging from -78° C to 25° C.

The addition-elimination reaction (Wittig reaction) is conducted by using, as the base, sodium hydride, sodium hydrobromide, sodium alcoholate, n-butyl lithium, lithium diisopropyl amide, etc., in a solvent such as dimethyl sulfoxide, tetrahydrofuran, dimethoxy ethane, etc. at temperatures ranging from -78° C to 80° C for about 0.5 to 24 hours.

And, when the double bond is hydrogenated, the object compound can be obtained in accordance with a conventional method using a catalyst such as palladium-carbon, etc.

The elimination (hydrolysis) of the hydroxy-protecting group can be conducted under the conditions of

conventional ester hydrolysis, but, when the product is unstable against oxygen under basic conditions, the reaction is conducted under argon atmosphere to thereby obtain the desired hydrolyzate in a good yield.

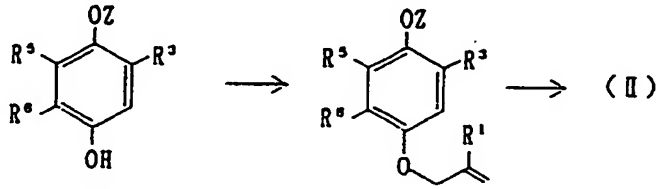
The acylation is carried out by using a desired acylating agent (acid anhydride, acid halogenide, etc.), when necessary, in the presence of a basic catalyst (preferably sodium hydride, potassium carbonate, pyridine and triethylamine) or an acid catalyst (sulfuric acid, hydrogen chloride, etc.), in an organic solvent (e.g. dimethylformamide, acetone, tetrahydrofuran) at temperatures ranging from about -10°C to 100°C for about 10 minutes to 15 hours.

Thus-obtained compound (I) can be isolated by conventional separation purification means (extraction, chromatography, recrystallization, etc.).

And, when the compound (I) exists in the state of diastereomer, the respective components can be isolated by the above-mentioned separation purification means.

And, when the compound (I) is an optically active compound, it can be resolved into d-compound and l-compound by conventional means for optical resolution.

The starting compound (II) can be synthesized by, for example, the method described below. More specifically, the monoacetate (IV) of hydroquinone is allowed to react with aryl halogenide in the presence of a base to lead to allyl ether (V), followed by subjecting (V) to Claisen rearrangement to give (II).



(IV) (V)

The compound (I) of this invention has an action of inhibiting production of 5-lipoxygenase-type metabolite [leucotrienes, 5-hydroperoxyeicosatetraenoic acid (HPETE), 5-hydroxyeicosatetraenoic acid (HETE), lipoxins, leucotoxins, etc.] and 12-lipoxygenase-type metabolite (12-HPETE, 12-HETE, etc.), and, therefore, the compound (I) can be used advantageously as an agent for ameliorating circulatory system, an anti-allergic agent, an agent acting on central nervous system.

The compound (I) can be safely administered, orally or *) singly or as a pharmaceutical composition prepared by mixing the compound (I) with a per se known pharmaceutically acceptable carrier, excipient, etc. (e.g. tablet, capsule, liquid, injection, suppository), to mammals (rat, horse, cow, monkey, human, etc.). While the dosage varies with subjects of administration, administration routes, symptoms, etc., in the case of, for example, administering orally to an adult patient suffering from diseases of circulatory system, it is convenient to administer with about 0.1 mg/kg to 20 mg/kg/body weight/dose, preferably 0.2 mg/kg to 10 mg/kg/body weight, once to three times a day.

Experimental Example 1:5-Lypoxygenase Inhibiting Action

In 0.5 mℓ of MCM (mast cell medium) was suspended 10^7 of rat basophilic leukemia (RBL-1) cells. To this suspension was added the test solution previously prepared [consisting of 0.5 mℓ of MCM, 50 μg of arachidonic acid, 10 μg of calcium ionophore A-23187 and the test compound (final concentrations 10 μM, 1 μM, 0.1 μM and 0.01 μM)], and the reaction was allowed to proceed at 37°C for 20 minutes. To the reaction mixture was added 4 mℓ of ethanol, which was shaken sufficiently, followed by leaving the resultant mixture standing for 10 minutes at room temperatures. The resultant mixture was subjected to centrifuge (2000 rpm) for 10 minutes, then the supernatant was separated. Thus-separated supernatant was concentrated to dryness under reduced pressure. To the concentrate was added 0.5 mℓ of a 60% aqueous methanol. 100μℓ Portion of this solution was taken and subjected to high performance liquid chromatography to perform quantitative determination of 5-HETE (5-hydroxyeicosatetraenoic acid). UV absorption of 5-HETE at 237 nm was measured with a UV absorption monitor. The inhibitory effect (IE) of 5-HETE is expressed by (1-b/a) x 100. In this formula, a means the height of the peak or the area of the peak in the

*) non-orally

case of containing no compound (I), while b means the height of the peak or the area of the peak in the case of containing the compound (I). The results revealed, as shown in Table 1, that the test compounds showed strong inhibitory action on the production of 5-HETE.

Table 1

Effect of Inhibiting 5-Lipoxygenase				
	% Inhibition (IE)			
Compound	10^{-5}M	10^{-6}M	10^{-7}M	10^{-8}M
5	100	100	57	0
6	100	100	52	4
10	100	99	98	12
12	100	100	90	46

Experimental Example 2

Through the descending aorta of a Wistar rat, 10 mℓ of blood was collected, under anesthesia, together with citric acid of a volume corresponding to 10%. PRP and PPP were respectively prepared, then they were mixed to make the number of platelets to be 10^9/mℓ. To 2.5 μℓ each of the test solutions prepared in advance (final concentrations of the test compounds : 100 μM, 10 μM, 1 μM and 0.1 μM) was added 0.225 mℓ of the platelet solution. The respective solutions were kept at 37° C for 5 minutes, to which was added 25 μℓ each of arachidonic acid solution (50 μg/mℓ) , then the respective mixtures were shaken immediately. The reaction was allowed to proceed at 37° C for 15 minutes, and there was added ethanol (1 mℓ) to stop the reaction. The reaction mixture was subjected to a centrifuge (2000 rpm) for 5 minutes. One mℓ of the supernatant was taken, which was mixed with 1 mℓ of water. 100μℓ of this mixture solution was subjected to high performance liquid chromatography to quantitatively determine 12-HETE. The detection was conducted at 240 nm. The calculation of the inhibition rate was conducted in a manner as in the case of 5-HETE. The results were shown in Table 2.

Table 2

12-Lipoxygenase Inhibitory Action				
	% Inhibition (IE)			
Compound	10^{-4}M	10^{-5}M	10^{-6}M	10^{-7}M
5	97	78	14	-
6	98	88	16	2
10	96	92	52	45
12	95	82	11	-
15	100	100	99	25
17	100	99	98	22
18	100	100	89	18
20	100	99	97	9
21	100	100	98	21
23	100	100	92	19
24	100	99	98	13
26	100	99	28	-
27	100	100	99	19
29	100	99	58	7
30	100	100	98	21
32	99	99	45	2
33	100	100	28	2
35	99	99	49	8
36	100	100	100	97
37	100	100	31	2
38	99	99	90	3
39	100	100	32	-
40	99	96	48	6
41	99	74	20	9

Examples

By the following Reference Examples, Examples and Formulation Examples of the compounds of the present invention, the present invention will be described in a more concrete manner, but the present invention is not to be limited thereto.

Reference Example 1

To a solution of 4-acetoxy-2,3,5-trimethylphenol [20 g (103 mmol.)] and methalyl chloride [10 g (110.4 mmol.)] in dimethylformamide (160 mℓ) was added potassium carbonate [15.2 g (110 mmol.)]. The mixture was stirred for 3 hours at 80°C under argon atmosphere. The reaction mixture was, after cooling, diluted with water, which was subjected to extraction with ethyl acetate. The extract was washed with water and dried, then the solvent was distilled off. The residue was crystallized from hexane to obtain the desired 4-acetoxy-2,3,5-trimethylphenyl-2-methylpropenylether [18.5 g (yield 72.4%)], m.p.44° to 45°C.

In a similar manner to the above, 4-acetoxy-2,3,5-trimethylphenyl allyl ether was synthesized. (yield 76.7%, m.p. 40° - 41°C).

Reference Example 2

In N,N-diethylaniline (100 mℓ) was dissolved 4-acetoxy-2,3,5-trimethylphenyl 2-methylpropenylether [16.2 g (6.5 mmol)], which was heated at 200°C for two hours. The reaction mixture was cooled and diluted with isopropyl ether, which was washed with 2N-HCℓ to remove N,N-diethylaniline. The remainder was

washed with a saturated aqueous solution of sodium hydrogencarbonate, which was dried, followed by distilling off the solvent. The residue was crystallized from isopropylether-hexane to obtain the desired 4-acetoxy-2-(2-methyl-2-propenyl)-3,5,6-trimethylphenol [14.9 g (yield 91.7%)] , m.p. 109°-110° C.

In a manner similar to the above, 4-acetoxy-2-allyl-3,4,6-trimethylphenol was synthesized. (Yield 94.6%, m.p. 117°-118° C)

Reference Example 3

In methylene chloride (100 mℓ) was dissolved 4-acetoxy-2-(2-methyl-2-propenyl)-3,5,6-trimethylphenol [30 g (40.3 mmol)]. To the solution was added at 0 C, in limited amounts, m-chloroperbenzoic acid [16.7 g (67.8 mmol)]. The reaction mixture was stirred for one hour, to which was added triethylamine (30 mℓ), followed by stirring for further one hour. The reaction mixture was washed with a saturated aqueous solution of sodium hydrogen carbonate, which was dried, followed by distilling off the solvent. The residue was crystallized from isopropyl ether - hexane to obtain the desired 5-acetoxy-2-hydroxymethyl-2,4,6,7-tetramethyl-2,3-dihydrobenzofuran [9.3 g (yield 87.4%, m.p. 98-99° C)].

Reference Example 4

To a methylene chloride solution (50 mℓ) of oxalyl chloride (2 mℓ) was added dropwise at -60° C dimethylsulfoxide (4 mℓ). The mixture was stirred for 10 minutes, to which was then added dropwise a methylene chloride (10 mℓ) of 5-acetoxy-2-hydroxymethyl-2,4,6,7-tetramethyl-2,3-dihydrobenzofuran [5.0 g (19 mmol)]. The reaction mixture was stirred for 15 minutes, to which was added triethylamine (15 mℓ), and the mixture was stirred for further 10 minutes. The reaction mixture was washed with water and dried, followed by distilling off the solvent. The residue was crystallized from isopropylether - hexane to obtain 5-acetoxy-2-formyl-2,4,6,7-tetramethyl-2,3-dihydrobenzofuran (yield 96.7%), m.p. 78-79° C.

Example 1

To a chloroform (15 mℓ) solution of 4-acetoxy-2-allyl-3,5,6-trimethylphenol [2.0 g(8.5 mmol)] was added dropwise, while stirring, bromine [1.36 g (8.5 mmol)]. To the mixture was then added triethylamine (0.3 mℓ), which was heated for two hours under reflux. The reaction mixture was cooled, washed with water, dried and then concentrated. The concentrate was crystallized from hexane to obtain 5-acetoxy-2-bromoethyl-4,6,7-trimethyl-2,3-dihydrobenzofuran (Compound 14) [2.5 g(yield 93.2%)].

In a manner similar to the above, 5-acetoxy-2-bromomethyl-2,4,6,7-tetramethyl-2,3-dihydrobenzofuran (Compound 13) was obtained from 4-acetoxy-3,5,6-trimethyl-2-(2-methyl-2-propenyl)phenol.

Example 2

To a dimethyl sulfoxide (5 mℓ) solution of 5-acetoxy-2-bromomethyl-2,4,6,7-tetramethyl-2,3-dihydrobenzofuran [1.5 g(4.58 mmol)] was added sodium cyamide [270 mg (5.5 mmol)], and the mixture was stirred at 80° C for 6 hours under argon atmosphere. The reaction mixture was, after cooling, diluted with water, which was subjected to extraction with ethyl acetate. The extract was washed with water and dried, followed by distilling off the solvent. The residue was purified by means of a silica gel column chromatography [hexane - isopropyl ether (2:1)] to obtain 5-acetoxy-2,3-dihydrobenzofuran (Compound 6) (350 mg) and 5-acetoxy-2-cyanomethyl-2,4,6,7-tetramethyl-2,3-dihydrobenzofuran (Compound 5)(158 mg).

Example 3

To a dimethylformamide (20 mol) solution of triethyl phosphonoacetate [2.7 g (12.1 mmol)] was added sodium hydride (content 60%)(504 mg), which was stirred for 15 minutes. To the reaction mixture was added a dimethyl formamide (5 mℓ) solution of 5-acetoxy-2-formyl-2,4,6,7-pentamethyl-2,3-dihydrobenzofuran [3.0 g (11.5 mmol)], and the mixture was stirred for further 30 minutes. The reaction mixture was diluted with water, which was subjected to extraction with ethyl acetate. The extract solution was washed

with water and dried, followed by distilling off the solvent. The residue was crystallized from hexane-isopropylether to obtain 3-(5-acetoxy-2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-2-yl)acetic acid ethyl ester (Compound 4)(3.5 g). In a manner similar to the above, Compound 8 was synthesized.

Example 4

To a methanol (10 mℓ) solution of ethyl ester of 3-(5-acetoxy-2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-2-yl) acrylic acid [3.5 g (10.5 mmol)] was added a solution of sodium hydroxide (1.0 g) in water (5 mℓ). The mixture was heated for two hours under reflux under argon atmosphere. The reaction mixture was cooled and neutralized with 2N-HCℓ, which was subjected to extraction with isopropyl ether. The extract solution was washed with water and dried, followed by distilling off the solvent. The residue was crystallized from tetrahydrofuran - ethyl acetate to afford the desired 3-(5-acetoxy-2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-2-yl)acrylic acid (Compound 3)(2.06 g). In a manner similar to the above, Compounds 7 and 10 were synthesized.

Example 5

To a solution of 3-(5-acetoxy-2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-2-yl)acrylic acid (1.0 g) in acetic acid (10 mℓ) was added 5% palladium-carbon (0.4 g), and the mixture was subjected to hydrogenation for two hours at 80 C. The catalyst was then filtered off, followed by distilling off the solvent. The residue was crystallized from tetrahydrofuran-isopropyl ether (IPE) to afford the desired 3-(5-hydroxy-2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-2-yl) propionic acid (Compound 2)(0.97 g). In a manner similar to the above, Compounds 9 and 12 were obtained.

Example 6

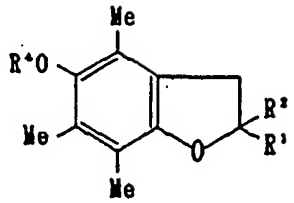
To a solution of 5-hydroxy-2-cyanomethyl-2,4,6,7-tetramethyl-2,3-dihydrobenzofuran in methanol (5 mℓ) was added a solution of sodium hydroxide (0.5 g) in water (5 mℓ). The mixture was heated for three hours under reflux under argon atmosphere. The reaction mixture was cooled and neutralized with 2N-HCℓ. The reaction product was extracted with ethyl acetate. The extract solution was washed with water, dried and concentrated, which was crystallized from ethyl acetate - isopropyl ether to afford the desired 2-(5-hydroxy-2,4,6,7-tetramethyl-2,3-dihydrobenzofuran-2-yl)acetic acid (Compound 1) (0.1 g).

Example 7

To a suspension of benzyltriphenyl phosphonium chloride [1.5 g (3.87 mmol)] in tetrahydrofuran (5 mℓ) was added dropwise, under ice-cooling, an n-butyl lithium hexane solution [(1.6 M) 24 mℓ], followed by stirring for 15 minutes. To the reaction mixture was added a solution of 5-acetoxy-2-formyl-2,4,6,7-tetramethyl-2,3-dihydrobenzofuran (1.0 g) in tetrahydrofuran (3 mℓ). The mixture was added water, which was subjected to extraction with ethyl acetate. The extract solution was washed with water and dried, then the solvent was distilled off. The residue was purified by means of a silica gel column chromatography [hexane-IPE(2:1)] to obtain the desired 5-acetoxy-2-cinnamoyl-2,4,6,7-tetramethyl-2,3-dihydrobenzofuran (Compound 11) (1.22 g).

Physico-chemical properties of the compounds obtained as above are shown in Table 3.

Table 3



Compd. No.	R^1	R^2	R^4	Yield (%)	m.p. (℃)	NMR (δ ppm) $CDCl_3$中
1	Me	$-CH_2CO_2H$	H	22.7	184-185	1.47(3H), 1.98(3H), 2.03(6H), 2.63(2H), 2.80(1H), 3.20(1H), 4.00(1H), 7.10(1H); in DMSO-d_6
2	Me	$-(CH_2)_2CO_2H$	H	96.3	164-165	1.33(3H), 1.85(2H), 1.97(3H), 2.03(6H), 2.27(2H), 2.73(1H), 2.95(1H), 3.50(1H), 7.20(1H); in DMSO-d_6
3	Me	$-CH=\underset{E}{CHCO_2H}$	H	74.6	211-212	1.53(3H), 2.05(6H), 3.03(2H), 3.60(1H), 5.83(1H), 6.92(1H), 7.10(1H); in DMSO-d_6
4	Me	$-CH=\underset{E}{CHCO_2Et}$	Ac	92.0	91- 92	1.27(3H), 1.58(3H), 1.95(3H), 2.00(3H), 2.13(3H), 2.30(3H), 3.07(2H), 4.17(2H), 6.02(1H), 7.05(1H)

5	Me	$-CH_2CN$	H	11.7	127-128	1.63(3H), 2.10(6H), 2.68(2H), 2.95(1H), 3.17(1H), 4.20(1H)
6	Me	$-CH_2Br$	H	26.8	101-102	1.60(3H), 2.12(9H), 2.88(1H), 3.27(1H), 3.48(2H), 4.15(1H)
7	Me	$-(CH=CH)_2-CO_2H$ (E)	H	82.9	204-206	1.50(3H), 2.03(9H), 3.00(2H), 3.90(1H), 5.87(1H), 6.37(2H), 7.15(1H); in DMSO-d_6
8	Me	$-(CH=CH)_2-CO_2Et$ (E)	Ac	87.8	—	1.27(3H), 1.57(3H), 1.97(3H), 2.03(3H), 2.13(3H), 2.33(3H), 3.05(2H), 4.17(2H), 5.87(1H), 6.37(2H), 7.20(1H)
9	Me	$-(CH_2)_4CO_2H$	H	74.0	143-144	1.28(3H), 1.50(6H), 1.93(3H), 2.00(6H), 2.20(2H), 2.72(1H), 2.93(1H), 7.20(1H) ;in DMSO-d_6
10	Me	$-CH=CH-Ph$ (E, Z)	H	95.1	—	1.52(3H), 1.87(3H), 2.00(3H), 2.07(3H), 2.88(1H), 3.18(1H), 4.08(1H), 5.90(1H), 6.48(1H), 7.23(5H)

EP 0 345 593 A1

11	Me	-CH=CH-Ph E, Z	Ac	95.2	—	1.57(3H), 1.90(6H), 1.97(3H), 2.30(3H), 2.88(1H), 3.20(1H), 5.90(1H), 6.50(1H), 7.25(5H)
12	Me	$-(CH_2)_2-Ph$	H	85.7	80- 81	1.47(3H), 1.98(2H), 2.13(6H), 2.15(3H), 2.73(2H), 2.87(1H), 3.05(1H), 4.08(1H), 7.23(5H)
13	Me	$-CH_2Br$	Ac	91.0	—	1.60(3H), 2.00(6H), 2.10(3H), 2.30(3H), 2.90(1H), 3.30(1H), 3.50(2H)
14	H	$-CH_2Br$	Ac	93.2	80- 81	2.00(6H), 2.10(3H), 2.30(3H), 3.13(2H), 3.53(2H), 4.97(1H)
15	Me	-CH=CH-CH_2-Ph Z	H	70.4	62- 63	1.57(3H), 2.11(3H), 2.16(3H), 2.18(3H), 3.06(1H), 3.20(1H), 3.56(1H), 3.69(1H), 4.16(1H), 5.56(1H), 5.75(1H), 7.15-7.35 (5H)

EP 0 345 593 A1

16	Me	-CH=CH-CH$_2$-Ph (Z)	Ac	74.9	oil	1.60(3H), 2.00(6H), 2.08(3H), 2.32(3H), 3.05(1H), 3.23(1H), 3.56(1H), 3.67(1H), 5.50(1H), 5.75(1H), 7.23(5H, m)
17	Me	-CH=CH-CH$_2$-Ph (E)	H	50.0	97- 98	1.52(3H), 2.10(3H), 2.12(3H), 2.14(3H), 2.95(1H), 3.10(1H), 3.38(2H), 4.15(1H), 5.74(1H), 5.84(1H), 7.10-7.40(5H, m)
18	Me	-CH=CH-Ph (E)	H	61.0	107-108	1.64(3H), 2.11(3H), 2.16(3H), 2.18(3H), 3.06(1H), 3.20(1H), 4.17(1H), 6.40(1H), 6.64(1H), 7.15-7.45(5H)
19	Me	-CH=CH-Ph (E)	Ac	92.0	103-105	1.63(3H), 1.97(3H), 2.02(3H), 2.15(3H), 2.30(3H), 3.00(1H), 3.23(1H), 6.33(1H), 6.65(1H), 7.20-7.50(5H)
20	Me	-(CH$_2$)$_3$-Ph	H	93.3	92- 93	1.37(3H), 1.72(4H), 2.07(6H), 2.10(3H), 2.62(2H), 2.77(1H), 2.97(1H), 4.07(1H), 7.00-7.35(5H)

21	Me	-CH=CH-(CH$_2$)$_2$-Ph (Z)	H	95.5	64- 65	1.45(3H), 2.07(6H), 2.12(3H), 2.61(4H), 3.00(2H), 4.08(1H), 5.48(1H), 6.14(1H), 7.00-7.30(5H)
22	Me	-CH=CH-(CH$_2$)$_2$-Ph (Z)	Ac	57.6	oil	1.47(3H), 1.93(3H), 1.98(3H), 2.07(3H), 2.30(3H), 2.40-2.80(2H), 3.00(2H), 5.38(1H), 5.68(1H), 7.00-7.35(5H)
23	Me	-(CH$_2$)$_4$-Ph	H	87.5	73- 74	1.20-1.80(6H), 1.03(3H), 1.07(6H), 2.12(3H), 2.60(2H), 2.77(1H), 2.97(1H), 4.08(1H), 7.00-7.35(5H)
24	Me	-CH=CH-Ph-4-OMe (Z)	H	97.0	oil	1.53(3H), 1.93(3H), 2.02(3H), 2.08(3H), 2.90(1H), 3.22(1H), 3.78(3H), 4.17(1H), 5.83(1H), 6.42(1H), 6.78(2H), 7.23(2H)
25	Me	-CH=CH-Ph-4-OMe (Z)	Ac	81.1	oil	1.53(3H), 1.92(6H), 1.97(3H), 2.27(3H), 2.90(1H), 3.22(1H), 3.77(3H), 5.83(1H), 6.42(1H), 6.77(2H), 7.20(2H)

EP 0 345 593 A1

26	Me	$-(CH_2)_2$-Ph-4-OMe	H	93.8	77- 78	1.47(3H), 1.65-2.10(2H), 2.13(6H), 2.15(3H), 2.40-2.80(2H), 2.83(1H), 3.05(1H), 3.78(3H), 4.10(1H), 6.78(2H), 7.10(2H)
27	Me	-CH=CH-Ph-3-OMe (Z)	H	98.0	oil	1.53(3H), 1.90(3H), 2.02(3H), 2.08(3H), 2.90(1H), 3.22(1H), 3.67(3H), 4.17(1H), 5.90(1H), 6.48(1H), 6.65-7.30(4H)
28	Me	-CH=CH-Ph-3-OMe (Z)	Ac	92.6	oil	1.53(3H), 1.88(6H), 1.95(3H), 2.90(1H), 3.23(1H), 3.67(3H), 5.88(1H), 6.47(1H), 6.60-6.90(3H), 7.05-7.30(1H)
29	Me	$-(CH_2)_2$-Ph-3-OMe	H	84.2	79- 80	1.47(3H), 1.70-2.10(2H), 2.10(6H), 2.13(3H), 2.40-2.80(2H), 2.83(1H), 3.05(1H), 3.77(3H), 4.10(1H), 6.60-6.85(3H), 7.10-7.30(1H)

30	Me	-CH=CH-Ph-4-F (Z)	H	94.6	oil	1.53(3H), 1.85(3H), 2.03(3H), 2.07(3H), 2.90(1H), 3.20(1H), 4.20(1H), 5.85(1H), 6.43(1H), 6.75-7.10(2H), 7.10-7.30(2H)
31	Me	-CH=CH-Ph-4-F (Z)	Ac	88.8	oil	1.55(3H), 1.83(3H), 1.90(3H), 1.93(3H), 2.27(3H), 2.90(1H), 3.22(1H), 5.87(1H), 6.42(1H), 6.90(2H), 7.20(2H)
32	Me	$-(CH_2)_2$-Ph-4-F	H	79.6	76- 77	1.47(3H), 1.70-2.10(2H), 2.10(6H), 2.13 (3H), 2.40-2.80(2H), 2.83(1H), 3.05(1H) 4.10(1H), 7.10(4H)
33	Me	-CH=CH-Ph-4-Me (Z)	H	96.5	oil	1.53(3H), 1.90(6H), 1.97(3H), 2.28(3H), 2.33(3H), 2.90(1H), 3.22(1H), 5.87(1H), 6.47(1H), 6.95-7.25(4H)
34	Me	-CH=CH-Ph-4-Me (Z)	Ac	91.1	oil	1.53(3H), 1.90(3H), 2.00(3H), 2.07(3H), 2.88(1H), 3.20(1H), 4.10(1H), 5.87(1H), 6.43(1H), 6.90-7.30(4H)

EP 0 345 593 A1

35	Me	$-(CH_2)_2$-Ph-4-Me	H	80.5	106-107	1.47(3H), 1.70-2.10(2H), 2.10(6H), 2.13(3H), 2.40-2.80(2H), 2.83(1H), 3.05(1H), 4.10(1H), 7.10(4H)
36	Me	$-CH=\underset{Z}{CH}-(CH_2)_2Me$	H	41.5	oil	0.91(3H), 1.40(2H), 1.52(3H), 2.12(6H), 2.17(3H), 2.19(2H), 3.04(2H), 3.16(1H), 4.16(1H), 5.38(1H), 5.68(1H)
37	Me	$-(CH_2)_4Me$	H	90.4	59- 60	0.88(3H), 1.29(6H), 1.39(3H), 1.68(6H), 2.10(6H), 2.13(3H), 2.81(1H), 2.97(1H), 4.14(1H)
38	Me	$-CH=\underset{Z}{CH}-(CH_2)_6Me$	H	49.7	oil	0.88(3H), 1.26(10H), 1.51(3H), 2.12(6H), 2.14(3H), 2.20(2H), 3.04(2H), 3.16(1H), 4.15(1H), 5.38(1H), 5.66(1H)
39	Me	$-(CH_2)_6Me$	H	83.3	69- 70	0.88(3H), 1.26(14H), 1.39(3H), 1.70 (2H), 2.10(6H), 2.13(3H), 2.81(1H), 2.97(1H), 4.13(1H)

40	Me	-CH=CH-(CH$_2$)$_{10}$Me Z	H	45.8	oil	0.88(3H), 1.25(18H), 1.51(3H), 2.11 (6H), 2.14(3H), 2.20(2H), 3.04(2H), 3.16(1H), 4.14(1H), 5.38(1H), 5.66(1H)
41	Me	-(CH$_2$)$_{12}$Me	H	84.6	67- 68	0.88(3H), 1.25(22H), 1.39(3H), 1.68 (2H), 2.10(6H), 2.13(3H), 2.81(1H), 2.97(1H), 4.14(1H)

Me: Methyl, Ac: Acetyl, Ph: Phenyl

Formulation Examples

A) Soft capsule	
(1) Compound 3	50 mg
(2) Corn oil	100 mg
	total 150 mg

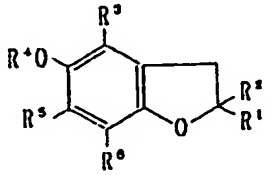
By a conventional method, (1) and (2) were mixed, which was filled in a capsule.

B) Tablet	
(1) Compound 10	50 mg
(2) Lactose	30 mg
(3) Corn starch	10.6 mg
(4) Corn starch (paste)	5 mg
(5) Magnesium stearate	0.4 mg
(6) Carboxymethyl cellulose sodium	20 mg
	total 116 mg

By a conventional method, these were mixed, which was tableted by a tablet machine.

Claims

1. A compound of the formula:



wherein R^1 is hydrogen or a lower alkyl; R^2 is methyl which is substituted by a carboxy, alkoxycarbonyl, cyano, halogen, aryl or heterocyclic group or C_{2-15} chain-like hydrocarbon residue having no lower alkyl at the a-position which may be substituted by a carboxy, alkoxycarbonyl, cyano, halogen, aryl or heterocyclic group; R^3 is a lower alkyl; R^4 is hydrogen or acyl; and R^5 and R^6 each is a lower alkyl or lower alkoxy, or R^5 and R^6 combined are butadienylene or a salt thereof.

2. The compound according to claim 1, wherein R^1 is hydrogen or C_{1-3} alkyl.

3. The compound according to claim 1, wherein R^2 is methyl substituted by carboxy, cyano or halogen.

4. The compound according to claim 1, wherein R^2 is methyl substituted by phenyl, thienyl, pyridyl, imidazolyl, thiazolyl or morpholino which may be further substituted by C_{1-20} alkyl, substituted C_{1-3} alkyl, C_{2-4} alkyl, hydroxy, halogen, nitro, formyl, C_{1-3} alkoxy, carboxy, trifluoromethyl, di-C_{1-3} alkylamino, C_{5-7} cycloalkyl or C_{1-3} alkylthio.

5. The compound according to claim 1, wherein R^2 is C_{2-15} alkyl or C_{2-15} alkenyl which may be substituted by carboxy, C_{1-3} alkoxycarbonyl or phenyl which may be substituted with halogen, C_{1-3} alkyl, C_{1-3} alkoxy or hydroxy.

6. The compound according to claim 1, wherein R^3 is C_{1-6} alkyl.

7. The compound according to claim 1, wherein R^4 is hydrogen or C_{1-10} alkanoyl.

8. The compound according to claim 1, wherein R^5 and R^6 are each C_{1-6} alkyl or C_{1-3} alkoxy.

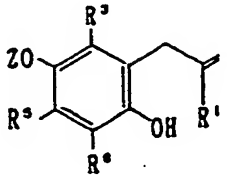
9. The compound according to claim 1, wherein R^1 is methyl; R^2 is C_{2-6} alkyl or C_{2-6} alkenyl which is substituted by phenyl which may be substituted by C_{1-3} alkyl, C_{1-3} alkoxy or halogen; R^3 is methyl; R^4 is hydrogen; and R^5 and R^6 are each methyl.

10. The compound according to claim 1, which is 5-hydroxy-2-cinnamoyl-2,4,6,7-tetramethyl-2,3-dihydrobenzofuran.

11. The compound according to claim 1, which is 5-hydroxy-2-phenylethyl-2,4,6,7-tetramethyl-2,3-dihydrobenzofuran.

12. The compound according to claim 1, which is 5-hydroxy-2-(1-(Z)-pentenyl)-2,4,6,7-tetramethyl-2,3-dihydrobenzofuran.

13. A method of producing the compound according to claim 1, which comprises reacting a compound of the formula:



(II)

wherein R^1, R^3, R^5 and R^6 are of the same meaning defined as above, Z is hydrogen or hydroxyl-protecting group, with halogen molecule in the presence of a base to cause ring-closure, or reacting the compound with a peracid, followed the ring closed compound with an oxidizing agent and reacting the resulting compound with a compound of the formula: $(C_6H_5)_3P^{\oplus}R^{2'}X^{\ominus}$ wherein X is halogen and $R^{2'}$ is a chain-like hydrocarbon residue whose carbon number is less by one than that of R^2, and when desired, subjecting the resultant to deprotection, acylation, hydrogenation or/and substituent-exchange reaction.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 89 10 9679

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
Y	CHEMICAL ABSTRACTS, vol. 108, no. 10, 7th March 1988, page 445, abstract no. 82107a, Columbus, Ohio, US; & JP-A-62 169 726 (YOSHITOMI PHARMACEUTICAL IND. LTD. et al.) 25-07-1987 * Abstract * ---	1-13	C 07 D 307/79 C 07 D 307/92 // A 61 K 31/34
Y	CHEMICAL ABSTRACTS, vol. 110, 1989, 27th February 1989, page 630, abstract no. 75294x, Columbus, Ohio, US; & JP-A-63 88 173 (KURARAY CO., LTD) 19-04-1988 * Abstract * ---	1-13	
Y,X	CHEMICAL ABSTRACTS, vol. 105, no. 23, 8th December 1986, page 510, abstract no. 207914h, Columbus, Ohio, US; K.U. INGOLD et al.: "A new vitamin E analog more active than alpha-tocopherol in the rat curative myopathy bioassay", & FEBS LETT. 1986, 205(1), 117-20 * Abstract * ---	1-13	
X,Y	CHEMICAL AND PHARMACEUTICAL BULLETIN, vol. 30, no. 8, August 1982, pages 2797-2819, Tokyo, JP; K. OKAMOTO et al.: "Synthesis of quinones having carboxy- and hydroxy-alkyl side chains, and their effects on rat-liver lysosomal membrane" * Page 2798, compound XVb * --- -/-	1-13	TECHNICAL FIELDS SEARCHED (Int. Cl.4) C 07 D 307/00

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	25-08-1989	ALLARD M.S.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P0401)

European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 89 10 9679

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
P,X	JOURNAL OF ORGANIC CHEMISTRY, vol. 54, no. 3, 3rd February 1989, pages 560-569, American Chemical Society, Easton, US; S. BROWNSTEIN et al.: "Chiral effects on the 13C resonances of alpha-tocopherol and related compounds. A novel illustration of Newman's "rule of six"" * Whole article *	1-13	

TECHNICAL FIELDS SEARCHED (Int. Cl.4)

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	25-08-1989	ALLARD M.S.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P0401)